NTP
National Toxicology Program

CERHR Evaluation Concept: Potential Developmental Effects of Cancer Chemotherapy during Pregnancy

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Nomination

- Nominated by NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)

- Concept developed in consultation with experts at:
  - National Cancer Institute (NCI)
  - National Institute of Child Health and Development
  - Center for Drug Evaluation and Research, Food and Drug Administration (FDA)
  - National Comprehensive Cancer Network (NCCN)

The New York Times

With Child, With Cancer

By PAMELA PAUL
Published: August 29, 2008

LIZETTE IRVIN, HEAVILY PREGNANT, reclined on a hospital bed, relaxed, considering the circumstances. A bag of fluid dripped into her blood through an IV line as Irvin sucked on ice cubes, trying to pass the time. The ice helped to minimize the metallic taste and heat in her mouth from 5-fluorouracil, an antimetabolite, which entered her bloodstream via a catheter inserted in her chest. It was June 16, Irvin's fourth round of chemotherapy. She was 32 week pregnant and had breast cancer.

Enlarge This Image

Dan Winters

Lizette Irvin had four rounds of chemotherapy while pregnant.

Before she left the chemo suite at the M. D. Anderson Cancer Center in Houston, Irvin, who is 36 years old, was hooked up to a portable pump that slowly released doxorubicin — "the red devil," a drug so toxic it can cause third-degree burns — into her body over the next 72 hours. During that time, her daughters, Madeline, 4, and Noelle, 2, stayed at her in-laws in part because Irvin feared that Noelle, "the clingy one," might accidentally tear out her IV.

It was Noelle's clambering on her mother that first alerted Irvin to a tender lump in her left breast last November. Irvin nearly called off her mammogram appointment when a home pregnancy test showed up positive in December. Because pregnant women typically experience

Background and Rationale

- 1/6000 to 1/1000 pregnant women are diagnosed with cancer
  - Frequency expected to increase as women postpone having children to later ages
- Chemotherapy is a common component of cancer treatment
  - Most agents are FDA Pregnancy Category D
    - Investigational or post-marketing data show risk to fetus
  - General medical opinion on chemotherapy use during pregnancy:
    - Avoid 1st trimester exposure because it is the period of major organogenesis
    - Treatment in 2nd and 3rd trimesters presents minimal risk to fetus

Background and Rationale (continued)

- A thorough systematic assessment of pregnancy outcomes following chemotherapy during pregnancy has not been published
- Some reviews have been published, but are generally limited to specific cancer types or chemotherapy agents
- A large literature, more than 500 papers on more than 50 agents, is available on pregnancy outcomes following chemotherapy
- Approximately 1000 to 6000 pregnant women are diagnosed with cancer per year in the United States

Specific Aim of the NTP Monograph

- To review the evidence for developmental effects of exposure to cancer chemotherapy *in utero*
  - Main focus will be clinical data in humans
  - Clinical data will be supplemented with biomedical and toxicological literature in animals
  - Goal:
    - To provide clinicians, patients, and researchers with a comprehensive review of the incidence and types of adverse effects observed in humans exposed *in utero* to cancer chemotherapy
    - Not intended to be a clinical guidance document

Key Objectives

- To identify the complete published scientific literature on chemotherapy during pregnancy in humans
    - Breast, hematopoietic system, lymphatic system, ovarian, cervical, skin, and thyroid cancers
- To critically evaluate the strength and consistency of this literature on embryo, fetal, and postnatal outcomes in humans by
    - Cancer type
    - Chemotherapeutic agent
    - Trimester of exposure
- To develop weight of evidence conclusions on the occurrence of adverse effects at different gestational stages by agent
- To identify data gaps and research needs for evaluating the effects of exposure to cancer chemotherapeutics *in utero*

Proposed Approach:
Preparation of NTP Monograph

- Review published literature on pregnancy outcomes and follow-up of offspring of women treated with cancer chemotherapy during pregnancy
  - Primary sources: case reports, case series, clinical trials, and cohort studies
  - Secondary sources: review papers and book chapters
- Develop summary tables by chemotherapy agent including trimester of exposure, pregnancy complications, and pregnancy outcome
- Include information regarding placental transfer of agent and known/proposed mechanism of action of agent to cause adverse effects
- Develop weight of evidence conclusions on the occurrence of adverse effects at different gestational stages by agent

Proposed Approach:

Scientific Development of NTP Monograph

- Scientific input obtained through:
  - Technical advisors
    (e.g., oncologists, obstetricians/gynecologists, and pediatricians)
  - Public
    - Federal Register notice
    - Notifications about the evaluation by NTP email listserv and NTP newsletter
  - Interagency review

Proposed Approach:

Peer Review and Release of NTP Monograph

- Tentatively scheduled for Summer of 2011
- Public comment
- Peer Review
  - *ad hoc* expert panel
  - Public meeting
  - Attendance by a BSC member
- Finalize the NTP Monograph

Significance and Expected Outcomes

The proposed NTP Monograph will:

- Provide a thorough survey and critical scientific evaluation of pregnancy outcomes of women treated with cancer chemotherapy during gestation
  - Useful to physicians, their patients and researchers by providing:
    - Comprehensive summary tables of the published clinical literature by agent
      - Including trimester of exposure, pregnancy outcome and follow-up on offspring (if available)
    - Text organized by cancer type
- Highlight registries of pregnant cancer patients, and studies that follow-up on offspring exposed *in utero* to cancer chemotherapy, including clinical trials
- Identify research needs

Questions or Comments?

Example of summary table: Trastuzumab (partial table)

Study type	# of cases	Cancer type	Timing*	Co-treatment (timing)	Labor, route	Fetal age at delivery	Pregnancy outcome	Follow Up (Y/N)
Case report	1	Breast	PC, 1st	None	C-section	39 wk	Male infant (3,550 g): normal. At 14 mo of age, normal growth and development.	Y
Case report	1	Breast	PC, 1st	None	NA	NA	Ectopic pregnancy: cervico-isthmic implantation. Elective abortion.	NA
Case report	1	Breast	3rd	Vinorelbine (3rd)	Vaginal	34 wk	Oligohydramnios. Male infant (5 lb, 11oz **[2,585 g]**): normal at birth and 6 mo of age.	Y
Case series	2	Breast	2nd	None	C-section	29 wk	Female infant (1220 g): Respiratory distress syndrome, conductive hearing loss (resolved). Mild hypertonia and hyperreflexia (resolved) and minimal tightening of left Achilles tendon.	Y
		Breast	PC, 1st	None	Vaginal	39 wk	Female infant (2.94 kg **[2,940 g]**): normal. Gastroenteritis at 3, 8, and 11 mo of age (resolved).	Y

*Timing of exposure = PC, immediately prior to conception; 1st, 2nd, and 3rd trimester.